

## REMARKS

Claims 1, 3-12, 14-32 will be in the application for prosecution after entry of the above amendments. Please note that the originally filed claims were replaced by a new set of claims under PCT Article 34. The above amendments are provided with indicators on the basis that the replacement claims are not original and therefore have been indicated to be “previously presented” unless they are being “currently amended”.

The amendments to the specification are in response to the International Preliminary Report on Patentability dated October 28, 2005. The Applicants intend to place the application in condition for allowance. The reasons for the amendments are discussed below.

### **Amendments to the Specification**

Page 6 has been amended at lines 25-28 to agree with the results of Tables 3 and 4, which report results of tests using SELDI (Surface Enhanced Laser Desorption/Ionization) technology. In the as-filed application, the results of ELISA testing of the three monoclonal antibodies using purified UTI standard lots are reported. The SELDI testing being considered more accurate, amendments were made to the original description. The PCT Examiner considered these amendments to go beyond the application as filed. However, the present amendments are supported by the reported SELDI data and do not differ significantly from the original tests. It will be seen in Tables 3 and 4 (the SELDI results) that all of the three monoclonal antibodies bind preferably to uristatin and uristatin-1 and -2. They differ in their ability to bind other UTIs Tamm-Horsfall protein (THP) and the pro-inhibitors. More specifically, Mab 420-5D11, was found to bind strongly to THP and Mab 421-3G5 binds also to other UTIs, but not to the pro-inhibitors. As amended, the page 6 discussion is substantially the same as the as-filed application, differing mainly on omitting specific reference to Mab 421-5G8 which binds strongly to the uristatin and less strongly to other UTIs.

Page 10 is of particular importance since in Example 1 the composition of the immunogen used to raise monoclonal antibodies was incorrectly reported in the as-filed application. This was discovered later and the composition was corrected in the Article 34 amendments. The preliminary examination report considered the change to be beyond the scope of the as-filed application, which it was. However, the incorrect composition cannot be permitted to remain in the application. Consequently, the Applicants have deleted the entire

sentence containing the incorrect composition. They have added the lot number of the purified UTI that was actually used as the immunogen to raise monoclonal antibodies. The composition of the immunogen at the time of its use was believed to be predominantly all uristatin (17 kDa). It was used as an immunogen because it was hoped to produce monoclonal antibodies having the ability to detect specific UTIs, which potentially could provide improved precision in clinical studies. (See the discussion at page 3, lines 17-32). The present inventors are believed to be the first to raise monoclonal antibodies against purified uristatin and to investigate their use.

One of the named inventors provides the attached declaration under 37 C.F.R. 1.132 regarding the error in reporting the composition of the immunogen reported in Example 1. In brief, Dr. Pugia shows that the immunogen was lot 157-90 and that its composition was predominantly uristatin (17 kDa). The composition of lot 20-120, which was erroneously reported, was predominantly bikunin (35 kDa) and higher molecular weight materials. Therefore, to delete the reported error and to place the correct information in the record, the amendments have been made and supported by Dr. Pugia's declaration.

On page 15, the word "as" was replaced in the Article 34 amendments with the words "even though" in order to correct a possible inconsistent interpretation of the sentence at lines 19-22. During the preliminary examination, the Examiner objected to this change. Consequently, in the above amendment the latter section of the sentence has been deleted. The revised sentence and the one following are sufficient to make the point.

On page 16, the word "not" was inserted at line 7 to correct what was believed to be an obvious error in meaning since the sentence otherwise appeared to be opposite to the previous sentence. In view of the objection raised by the Examiner, the sentence at lines 7-8 has been deleted to avoid misunderstanding of the Applicants' meaning.

### **Amendments to the Claims**

Claims 1 and 12 have been amended to correct an error noted by the Examiner in the International Preliminary Report on Patentability ("IPRP").

Claims 2 and 13 have been canceled since the composition was considered to extend beyond the application as filed. The composition reported in the as-filed application was discovered to be incorrect and consequently was replaced in the Article 34 amendments. See also the discussion above and the accompanying declaration related to this matter. Since Claims

2 and 13 have been canceled, Claims 3, 5, 7, 9, and 14 have been amended to correct their dependency.

Claims 6 and 16 have been amended to include only those UTIs shown in Tables 3 and 4 to be strongly bound to monoclonal antibody ATCC 420-5D11.5G8.1E4. Claims 8 and 17 have been amended in a similar manner.

The Applicants note that Tables 3 and 4 were obtained from a high sensitivity method of determining the binding of antibodies to various proteins (SELDI). The results indicate binding of many protein forms, but for purposes of the present claims only those from mostly strongly bound were included. One exception is found in regard to Mab 421-3G5, which did not bind to bikunin in Table 3, but did bind strongly in Table 4. This difference cannot be explained at this time. However, it should be realized that while Table 3 reports the results using purified UTI standards, Table 4 reports the results with purified patent samples. It is believed that the difference in the source of tested samples may account for the differences that are reported.

### **Novelty**

The IPRP examiner considered Claims 1, 9, 12, 20, 21, and 25 to lack novelty in view of five disclosures; the Applicants disagree for the following reasons:

Trefz et al. produced monoclonal antibodies from “high molecular weight ITI”, or what is referred to in the present application as pro-inhibitors. These are urinary trypsin inhibitor precursors and not the purified uristatin (17 kDa) used by the Applicants to produce their monoclonal antibodies.

In U.S. 6,242,197 Papuashvili reported in her Example 1 that monoclonal antibodies were raised against UTI, which is defined at column 3, lines 17-20 as having a molecular weight of about 44 kDa. Thus, Papuashvili raised antibodies against what the Applicants call “bikunin” and not to the lower molecular weight uristatin used by the Applicants.

Kobayashi et al. also refers to UTI as bikunin (40 kDa). They do not refer to the lower molecular weight uristatin used by the Applicants to raise monoclonal antibodies.

In published U.S. application 2003/0190732 Josic raised monoclonal antibodies against bikunin, but he also does not refer to uristatin. The Applicants believe that they have identified and investigated uristatin before many, if not all, of the workers in the field.

Pugia et al. reported making polyclonal antibodies from bikunin (33 kDa) and not monoclonal antibodies from purified uristatin.

Inasmuch as the references cited by the IPRP examiner did not report making monoclonal antibodies from uristatin, the Applicants submit that their claims do possess novelty.

**Inventive Step**

Only Claims 1, 9, 12, 20, 21, and 25 were considered to lack inventive step, the IPRP examiner suggesting that further evidence relating to a "technical effect" may be required. The Applicants have carried out clinical studies using their monoclonal antibodies and comparing the results with other methods of determining the presence of inflammation in humans. This evidence is available to show inventive step and unobviousness over the prior art, if required during prosecution.

In view of the above amendments and remarks the Applicants believe that the claims should be in condition for allowance. The Examiner is invited to contact the Applicants' attorney at the telephone number provided below if further amendment is considered necessary.

Respectfully submitted,

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Date

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